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ORIGINAL PAPER

Plasma KIM-1 and interleukin-18 are superior biomarkers for diagnosing and stratifying risk in type 1 acute cardiorenal syndrome

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ABSTRACT

Introduction and aim. Acute cardiorenal syndrome (CRS) is a condition in which acute cardiac dysfunction leads to acute kidney injury (AKI), resulting in high morbidity and mortality rates. This study aimed to assess the diagnostic and prognostic value of plasma kidney injury molecule 1 (KIM-1) and interleukin-18 (IL-18) levels in acute CRS compared to acute heart failure (AHF) and healthy controls.

Material and methods. A case-control study was conducted with 90 participants divided into three groups: control (n=30), AHF (n=30), and acute CRS (n=30). Renal function parameters (serum creatinine, blood urea nitrogen, estimated glomerular filtration rate) and plasma biomarkers (KIM-1, IL-18) were measured. A receiver operating characteristic curve analysis was used to evaluate diagnostic performance and logistic regression was used to identify predictors of disease outcomes.

Results. Plasma KIM-1 and IL-18 levels were significantly higher in the acute CRS group than in the AHF and control groups. KIM-1 demonstrated superior diagnostic accuracy (the area under the curve (AUC)=1.000) with 100% sensitivity and specificity, while IL-18 also performed well (AUC=0.96, sensitivity=96%, specificity=97%). ROC analysis identified plasma KIM-1 and IL-18 cut-off values of >72.78 pg/mL and >254.8 pg/mL, respectively, which may be used as thresholds for early diagnosis and risk stratification. Logistic regression analysis revealed that plasma KIM-1 was a significant predictor of adverse outcomes (OR=3.5, 95% CI 1.50–8.49, p=0.003), while IL-18 also contributed to risk stratification (OR=1.06, 95% CI 1.04–1.125, p=0.03). These adverse outcomes included progression to kidney disease. However, these findings require validation in an independent cohort to confirm reproducibility and generalizability.

Conclusion. KIM-1 and IL-18 are highly effective biomarkers for diagnosing and stratifying the risk of acute CRS, outperforming traditional markers of renal function. Their clinical integration could enable early detection and personalized treatment, thus improving patient outcomes. However, more studies with larger cohorts, serial measurements, and independent validation are warranted.

Keywords. acute cardiorenal syndrome, AHF, AKI, IL-18, KIM-1

Introduction

Acute cardiorenal syndrome (CRS) represents a complex and bidirectional interplay between the heart and kidneys, in which acute cardiac dysfunction precipitates acute kidney injury (AKI) or exacerbates preexisting renal dysfunction.[1] Type 1 CRS, characterized by acute de-

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compensated heart failure leading to AKI, is associated with a high morbidity and mortality burden, affecting more than 30% of hospitalized patients with acute heart failure (AHF).[2,3] The intricate pathophysiology of CRS involves hemodynamic alterations, neurohormonal activation, systemic inflammation and oxidative stress, culminating in structural kidney damage and functional impairment.[4,5] Early identification and stratification of patients at risk of CRS are critical for improving clinical outcomes; however, this remains a challenge due to the overlapping presentation of cardiac and renal dysfunction and the limitations of traditional diagnostic tools.[6]

Recent advances in precision medicine underscore the limitations of conventional renal markers, such as serum creatinine and estimated glomerular filtration rate (eGFR). In addition to these markers, emerging biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and soluble ST2 are being investigated for early detection and risk stratification in cardiorenal syndrome.[7,8] For example, a study by Erdil highlights the role of advanced nanobiomaterials and innovative signaling approaches in cardiovascular disease.[9] Consequently, there has been growing interest in identifying new biomarkers that can provide more precise insights into the underlying pathophysiology of CRS.[6] Plasma biomarkers, such as kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18), have emerged as promising candidates in this context.[10] KIM-1 is a transmembrane glycoprotein expressed in renal proximal tubular cells in response to ischemic or toxic injury and has been validated as a sensitive marker of tubular injury in AKI.[11,12] Similarly, IL-18, a proinflammatory cytokine, plays a key role in mediating renal inflammation and apoptosis, making it a potential biomarker for detecting inflammatory kidney injury.[13,14]

Recent studies have highlighted the utility of KIM-1 and IL-18 in various renal pathologies, including AKI and chronic kidney disease (CKD), but their roles in CRS remain underexplored.[15] Given the dynamic interplay between cardiac and renal dysfunction in CRS, these biomarkers may offer valuable insights into both the structural and inflammatory aspects of kidney injury, thus complementing traditional renal function parameters. Furthermore, the integration of biomarkers into clinical practice has the potential to enhance risk stratification, allowing timely therapeutic interventions, and improving patient outcomes.[16,17] However, our study is novel in that it focuses specifically on the diagnostic and prognostic utility of plasma KIM-1 and IL-18 in type 1 CRS, where acute heart failure leads to acute kidney injury.

Aim

In this study, our aim was to evaluate the clinical utility of plasma levels of KIM-1 and IL-18 as diagnostic and prognostic biomarkers in patients with acute CRS. Specifically, we investigated their correlation with renal function parameters, the ability to differentiate CRS from AHF, and the predictive value of adverse outcomes. By comparing these biomarkers across the control, AHF, and CRS groups, we sought to provide novel information on their relevance to the pathophysiology and management of CRS. Furthermore, this study contributes to the growing body of evidence supporting biomarker-based approaches in cardiorenal syndromes, paving the way for more personalized and effective patient care.

Material and methods

Study design and participants

A case-control study was conducted between February 2023 and July 2024 at the (Al-Sadr Teaching Hospital in Najaf, Iraq), following approval from the Institutional Review Board (approval number: 34328). Written informed consent was obtained from all participants prior to inclusion, in accordance with the principles of the Declaration of Helsinki.[18] The sample size (n) was determined using the following formula to compare the two proportions in case-control studies.[19]

$$n = \left\{ \left(Z_{\{\frac{\alpha}{2}\}} + Z_{\{\beta\}} \right)^2 \cdot \left[p_{1(1-p_1)} + p_{2(1-p_2)} \right] \right\} / \{ (p_1 - p_2)^2 \}$$

- $Z_{\{\frac{\alpha}{2}\}} = 1.96$ for a 95% confidence level,
- $Z_{\{\beta\}} = 0.84$ for 80% power,
- $p_1 = 0.70$ (proportion of a specific marker in the CRS-1 group based on previous studies),
- $p_2 = 0.30$ (proportion in controls).

Ninety participants were divided into three groups: (i) control (n=30), (ii) AHF (n=30), and (iii) acute CRS (n=30). A sample size of 30 subjects per group was chosen based on previous biomarker studies in similar clinical settings. Although this is a preliminary investigation, the sample size provided sufficient power to detect statistically significant differences; however, future studies with larger cohorts are recommended. The inclusion criteria for the AHF and acute CRS groups were clinical, radiological, and laboratory evidence of acute cardiac dysfunction with or without concomitant AKI. Subjects were excluded if they had chronic dependence on dialysis, severe systemic illness (e.g., advanced liver disease or active malignancy), or recent exposure to nephrotoxic agents. Patients with AHF and CRS were recruited based on established diagnostic criteria, including the European Society of Cardiology guidelines for AHF and definition of type 1 CRS as acute cardiac dysfunction leading to renal impairment.[20,21] The classification of AKI among patients with acute CRS was performed using Kidney Disease: Improving Global

Outcomes (KDIGO) criteria, which define AKI based on an increase in serum creatinine of <0.3 mg / dL in 48 hours, an increase to ≥1.5 times the baseline within 7 days, or a reduction in urine output of <0.5 mL/kg/hour for at least 6 hours. Further stratification was performed using the same criteria, which categorize AKI severity based on serum creatinine changes and urine output over time.[22]

Data collection

Demographic details (age and sex) and relevant medical history were documented. Anthropometric measurements included body mass index (BMI), calculated as weight (kg) divided by the square of height (m).[23] Disease severity was assessed using clinical and echocardiographic parameters. Functional status in the AHF and CRS groups was classified using the New York Heart Association (NYHA) classification.[24] The duration of hospitalization was recorded in days for each patient. The left ventricular ejection fraction (EF) was assessed using two-dimensional transthoracic echocardiography (TTE) following the guidelines of the American Society of Echocardiography guidelines.[25]

Sample collection

Venous blood samples (5–7 mL) were collected from each participant by standard phlebotomy into serum separator tubes and plasma tubes of ethylenediaminetetraacetic acid. Samples were drawn under fasting conditions (if clinically feasible) or at a standardized time point immediately after admission. The tubes were centrifuged at 3,000×g for 10 min at 4°C and serum and plasma aliquots were stored at -80° C until the test.

Biochemical measurements

Renal function parameters, including serum creatinine and blood urea nitrogen (BUN), were measured using an automated chemistry analyzer (Beckman Coulter AU5800; Cat No. A18504, Beckman Coulter Inc., USA). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula:[26]

MDRD-2 (abbreviated) equation: GFR (expressed in ml/min/1.73 m^2)=$186\times[Pcr]^{-1.154}\times[age]^{-0.203}\times$[0.742 if the patient is female]

Plasma biomarkers, including KIM-1 and IL-18, were quantified using enzyme-linked immunosorbent assay (ELISA) kits. KIM-1 levels were measured using the human KIM-1 quantikine ELISA Kit (Cat No. DY1757-05, USA). This assay had a sensitivity of 0.1 pg/ml and an intra-assay coefficient of variation (CV)<6%. IL-18 levels were assessed using a human IL-18 high-sensitivity ELISA Kit (Cat No. BMS267-2, USA), which had a detection limit of 1.0 pg/ml and an inter-assay CV<8%. All biomarker measurements were performed in duplicate to ensure precision following the manufacturer's protocol.

Statistical analysis

GraphPad Prism 9 (GraphPad Software, Inc. Boston, MA, USA) was used to detect the effect of different groups (patients and controls) on study parameters. A t-test was used to compare the means. The chi-square test was used to compare the percentages (0.05 and 0.01 probability). Estimation of the correlation coefficient and multiple linear regression between variables. The sensitivity and secrecy of parameters in the patient and control groups for biomarkers were determined using receiver operating characteristic (ROC) curve analysis to maximize sensitivity and specificity. The Youden index was used to identify the optimal thresholds for each parameter.[27]

Results

Demographic characteristics of study groups

Table 1 shows the baseline characteristics of the control, AHF and acute CRS groups. No significant differences were observed in age (p=0.26), sex distribution (p=0.25) or BMI (p=0.16) between the groups, ensuring demographic comparability. The prevalence was higher in the AHF (73%) and Acute CRS (83%) groups than in the controls, but this difference was not statistically significant (p=0.5). The duration of hospitalization (p<0.001) and NYHA classification (p<0.001) showed significant differences, with acute CRS patients experiencing longer hospital stays and more severe functional impairment (70% in NYHA class IV). EF also decreased progressively between groups, with a significant decrease from control (60.77±4.30%) to AHF (41.70±5.08%) and acute CRS (34.73±2.49%) (P> 0.001). These findings reflect the increasing clinical severity from AHF to acute CRS, highlighting the class EF and NYHA as key indicators of disease progression.

Distribution and severity of AKI stages in patients with acute CRS

Table 2 and Figure 1 illustrate the distribution of AKI stages according to KDIGO criteria among patients with acute CRS. Most of the patients (76%) were classified as stage II AKI, while only 24% were classified as stage I. This finding highlights the prevalence of severe renal impairment in this cohort. Figure 1 provides a clear visual representation of this distribution, highlighting the significant proportion of stage II cases. These findings underscore the critical severity of kidney dysfunction in patients with acute CRS and have important implications for clinical management and prognosis.

Table 1. Baseline demographic and anthropometric characteristics of the control, AHF, and acute CRS groups[a]

Characteristic	Control n=30	AHF n=30	Acute CRS n=30	p
Age (years)				
Mean±SD	65.5±5.6	62.9±5.6	64.6±7.09	0.26 O[NS]
Range	55–75	55–73	55–75	
Sex				
Male, n (%)	14 (46%)	19 (63%)	13 (43%)	0.25 F[NS]
Female, n (%)	16 (54%)	11 (37%)	17 (57%)	
BMI (kg/m^2)				
Mean±SD	25.7±1.26	28.4±0.84	28.9±1.54	0.16 O[NS]
Range	23.6–28.4	27.1–29.7	25.4–30.2	
Smoking Status				
Non-Smoker, n (%)	-	8 (27%)	5 (17%)	0.5 F[NS]
Smoker, n (%)	-	22 (73%)	25 (83%)	
Duration of hospitalization				
≤ 7 days, n (%)	-	19 (63%)	0 (0.0 %)	<0.001 F[***]
>7 days, n (%)	-	11 (37%)	30 (100 %)	
NYHH classification				
Class I, n (%)	-	0 (0.0%)	0 (0.0 %)	<0.001 F[***]
Class II, n (%)	-	8 (27%)	0 (0.0%)	
Class III, n (%)	-	22 (73%)	9 (30 %)	
Class IV, n (%)	-	0 (0.0%)	21 (70 %)	
Ejection fraction %				
Mean±SD	60.77±4.30	41.70±5.08	34.73±2.49	<0.001 O ***
Range	59.16–62.37	39.80–43.60	33.80–35.66	

[a] n number of cases, SD – standard deviation, O one-way ANOVA, NS – not significant (p <0.05), F – Fisher's exact test

Table 2. Distribution of AKI stages (KDIGO criteria) among acute CRS patients

	AKI stagE (KDIGO)	
	Stage I, n (%)	Stage II, n (%)
AcutE CRS	7 (24%)	23 (76 %)

These findings are illustrated in Figure 1, which shows the proportional representation of the stages of AKI in patients with acute CRS. The dominance of stage II AKI is evident, highlighting the need for effective strategies to manage and monitor renal dysfunction in this high-risk group.

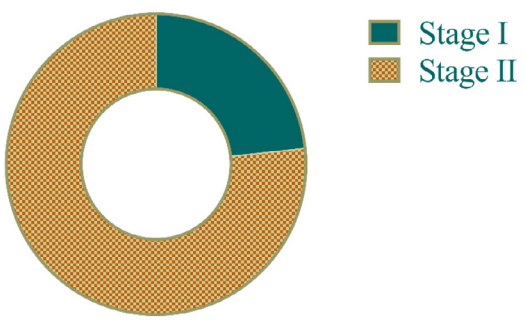

Fig. 1. Proportional representation of AKI stages (KDIGO criteria) in acute CRS patients

Renal function parameters among study groups

Table 3 and Figure 2 summarize renal function parameters, demonstrating progressive renal dysfunction from the control to the AHF and acute CRS groups. Blood urea levels were significantly elevated in acute CRS (41.2±18.1 mg/dL) compared to control (20.9±5.4 mg/dL) and AHF (25.4±9.3 mg/dL). Baseline and current serum creatinine levels followed a similar trend, with significant differences between all groups, highlighting the worsening of renal impairment in acute CRS (current serum creatinine: 2.64±0.53 mg/dL).

Table 3. Renal function markers in acute heart failure and cardio-renal syndrome patients a control comparison

Characteristic	Control	AHF	Acute CRS	p
BUN (mg/dL)				
Mean±SD	9.7±2.5 A	11.8±4.3 A	19.2±8.4 B	<0.001 O ***
Range	4.6–14.4	6.2–26.3	10.7–37.5	
Baseline serum creatinine (mg/dL)				
Mean±SD	0.85±0.08 A	0.9±0.06 B	1.14±0.08 B	<0.001 O ***
Range	0.72–0.99	0.89–1.09	1.02–1.26	
Current serum creatinine (mg/dL)				
Mean±SD	0.84±0.09 A	1.14±0.06 B	2.64±0.53 C	<0.001 O ***
Range	0.7–1.0	1.0 –1.23	1.65–3.4	
eGFR (mL/min/1.73 m^2)				
Mean±SD	78±13.9 A	69.3±10.3 B	55.1±9.6 C	<0.001 O ***
Range	54.9–112	51.6–86	41.7–73	

[a] n number of cases, SD – standard deviation, O one-way ANOVA, *** – significant at p <0.001, capital letters A, B, and C were used to indicate the level of significance following Tukey's multiple comparison test, similar letters indicate no significant difference, while different letters indicate significant differences, * the conversion factor (CF) to convert blood urea (BU) to blood urea nitrogen is 2.14

eGFR showed a significant decline, with the mean eGFR decreasing progressively from control (78±13.9 mL/min/1.73 m^2) to AHF (69.3±10.3 mL/min/1.73 m^2) and acute CRS (55.1±9.6 mL/min/1.73 m^2). Figure 2 visually represents this reduction in eGFR, highlighting the marked decline in renal function in acute CRS.

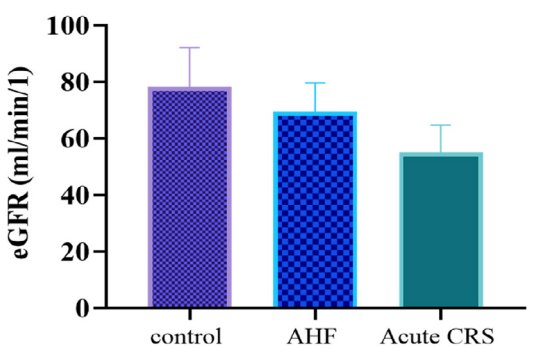

Fig. 2. Comparison of mean eGFR among study groups

Plasma biomarkers in study groups

Table 4 highlights the significant differences in plasma biomarkers (KIM-1 and IL-18) between the control, AHF and acute CRS groups. Plasma KIM-1 levels were markedly elevated in acute CRS (432.8±55.2 pg/mL) compared to AHF (63.8±27.2 pg/mL) and control (50.6±10.5 pg/mL), with, indicating severe kidney tubular injury in acute CRS. Similarly, plasma levels of IL-18 were significantly higher in the acute CRS (415±52 pg/mL) than in the AHF (258±41.6 pg/mL) and control (105.2±24.5 pg/mL) groups, reflecting increased inflammation associated with renal dysfunction.

Table 4. Comparison of plasma KIM-1 and IL-18 among the control, AHF, and acute CRS groups[a]

Characteristic		Control	AHF	Acute CRS	p
Plasma KIM-1 (pg/mL)					
	Mean±SD	50.6±10.5 A	63.8±27.2 B	432.8±55.2 C	<0.001 O ***
	Range	22.1–72.8	18.5–125	310–562	
Plasma IL-18 (pg/mL)					
	Mean±SD	105.2±24.5 A	258±41.6 B	415±52 C	<0.001 O ***
	Range	58–154	179–342	307–514	

[a] n number of cases, SD – standard deviation, O one-way ANOVA, *** – significant at p<0.001, capital letters A, B, and C were used to indicate the level of significance following Tukey's multiple comparison test, similar letters indicate no significant difference, whereas different letters indicate significant differences

Correlation analysis of biomarkers in cardiorenal syndrome

Correlation between plasma biomarkers (IL-18 and KIM-1) and renal function parameters (current creatinine and eGFR). Plasma levels of IL-18 showed a strong positive correlation with current creatinine levels (r=0.841, p<0.0001, Fig. 3A) and a significant negative correlation with eGFR (r=-0.604, p<0.0001, Fig. 3B). Similarly, plasma KIM-1 showed a robust positive correlation with current creatinine level (r=0.917, p<0.0001, Fig. 4A) and moderate correlations with eGFR (r=-0.594, p>0.0001, Fig. 4B). These findings suggest that plasma IL-18 and KIM-1 are closely associated with markers of renal dysfunction, highlighting their potential utility as reliable biomarkers for assessing the severity and progression of kidney injury. The negative correlation with eGFR further supports its relevance in reflecting a decline in renal function.

Diagnostic efficacy of biomarker in the studied groups

Figures 5A and 5B demonstrate the diagnostic utility of plasma levels of KIM-1 and IL-18 in identifying acute CRS. Plasma KIM-1 showed outstanding diagnostic performance with a cut-off value of >72.78 pg/mL, achieving 100% sensitivity and specificity with an area

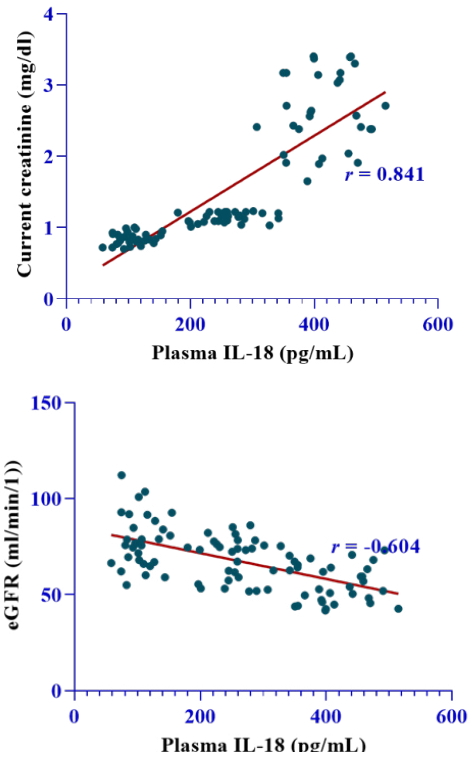

Fig. 3. A: Correlation between current creatinine and plasma IL-18, B: Correlation between eGFR and plasma IL-18

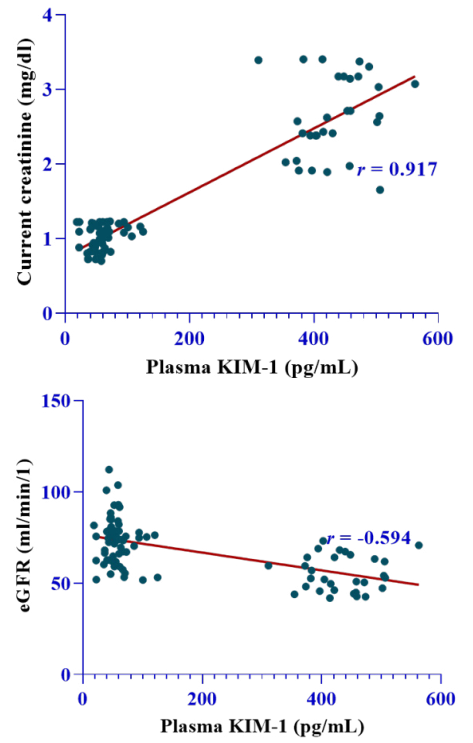

Fig. 4. A: Correlation between current creatinine and plasma KIM-1, B: The correlation between eGFR and plasma KIM-1 (all correlation coefficients (r) are statistically significant at p<0.0001, the strong positive correlations suggest that higher KIM-1 levels closely with increases in creatinine levels, indicating possible deterioration in renal function)

under the curve (AUC) of (1.000, p<0.001), as shown in Figure 5A. Similarly, plasma IL-18 showed a high diagnostic capability with a cut-off value of >254.8 pg/mL, yielding a sensitivity of 96% and specificity of 97%, with an AUC of (0.996, p<0.001), as depicted in Figure 5B.

These results highlight the exceptional diagnostic power of plasma KIM-1 and IL-18 as biomarkers of acute CRS, with plasma KIM-1 showing perfect discrimination. Both biomarkers demonstrated a robust potential for early detection and risk stratification in patients with acute CRS, supporting their clinical utility in improving outcomes through targeted interventions.

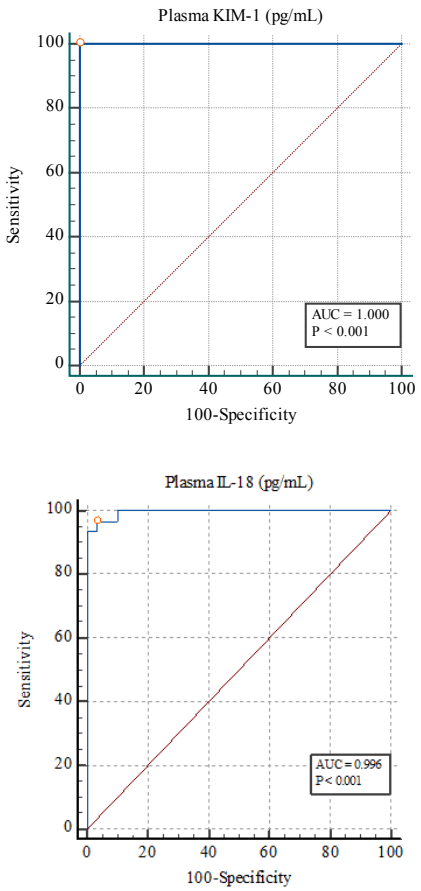

Fig. 5. A: The ROC curve for plasma KIM-1, B: The ROC curve for plasma IL-18

Statistical analysis of plasma KIM-1 and IL-18

Table 5 presents the logistic regression analysis of the plasma biomarkers KIM-1 and IL-18 as predictors of disease outcome, with model 1 achieving high explanatory power (R2=0.81, (p<0.0001). Plasma KIM-1 level demonstrated a significant positive association with disease outcome (B=1.27, OR=3.5), highlighting its strong predictive potential. Similarly, plasma IL-18 showed a significant, although weaker, association (B=0.06, OR=1.06) The model ROC AUC of 0.971 (95%CI: 0.911–0.995) reflects excellent discriminative ability, further corroborated by high classification accuracy for negative cases (93.33%), positive cases (90%), and overall accuracy (91.11%). These results emphasize the clinical utility of plasma KIM-1 and IL-18 levels as significant and complementary predictors of disease outcomes, and plasma KIM-1 emerging as a stronger predictor in the logistic model.

Table 5. Logistic regression analysis of biomarkers to predict disease outcome: evaluation of plasma KIM-1 and IL-18 as significant predictors, model 1 (R2=0.81) (p<0.0001)[a]

Variables	B (coef)	Wald	Odds ratio	95% CI for Odds Ratio	p
Plasma KIM-1 (pg/mL)	1.27	8.3	3.5	1.50 to 8.49	0.003**
Plasma IL-18 (pg/mL)	0.06	4.45	1.06	1.04 to 1.125	0.03*
ROC AUC	0.971 (95% CI: 0.911 to 0.995)				
Classification accuracy	Negative cases: 93.33%, Positive cases: 90%, Overall: 91.11%				

[a] B (coef) regression coefficient, CI – confidence interval, dependent variable current creatinine

Discussion

This study evaluated the clinical utility of plasma biomarkers, kidney function parameters, and disease severity indices to distinguish CRS from AHF and healthy controls. Additionally, we explored the prognostic potential of these biomarkers for predicting disease outcomes. Our findings demonstrated that plasma levels of KIM-1 and IL-18 are significantly associated with renal dysfunction and systemic inflammation. Integrating these biomarkers into clinical practice could revolutionize the management of acute CRS.

The progressive decline in renal function parameters, such as serum creatinine, BUN, and eGFR, is observed to reinforce the pathophysiological continuum from AHF to acute CRS. Acute CRS epitomizes a bidirectional interplay, in which cardiac dysfunction precipitates renal hypoperfusion, resulting in structural kidney damage and impaired filtration capacity.[28] Our study corroborates previous research that indicates that eGFR and serum creatinine level are critical markers of renal dysfunction, with progressive deterioration being a hallmark of CRS.[29,30]

However, although these traditional parameters are instrumental in reflecting established kidney injury, their diagnostic sensitivity in the early stages of CRS remains suboptimal.[6] This limitation arises from their inherent nonspecificity and delayed elevation following renal injury.[31] For example, the serum creatinine level may not rise until significant renal impairment has occurred, thus delaying timely diagnosis and intervention.[32]

Our findings are further aligned with those of other studies that highlight BUN as an adjunctive marker of renal dysfunction. Elevated BUN levels in acute CRS patients not only signify renal impairment, but also reflect

metabolic derangements associated with CRS.[33] The increase in BUN is indicative of reduced renal perfusion and neurohormonal activation, which contribute to the accumulation of uremic toxins.[34] The concurrent decline in eGFR and the increase in serum creatinine underscore the progressive deterioration of glomerular function, a critical aspect of the pathophysiology of CRS.

This study underscores the clinical utility of plasma KIM-1 and IL-18 as biomarkers for the early detection of renal injury and inflammation in acute CRS. KIM-1, a type I transmembrane glycoprotein expressed in proximal tubular cells, is markedly up-regulated after ischemic or toxic injury, and serves as a sensitive and specific indicator of tubular damage.[11,12] Elevated levels of plasma KIM-1 likely reflect tubular injury due to renal ischemia, as KIM-1 is up-regulated in response to tubular cell damage.[11] In our study, elevated plasma KIM-1 levels were significantly associated with acute CRS, demonstrating superior diagnostic accuracy (AUC=1.0), while our ROC analysis demonstrated exceptionally high AUC values for plasma KIM-1 (1.000) and IL-18 (0.996), these results should be interpreted with caution. The near-perfect discrimination may partly reflect overfitting due to our limited sample size and the absence of an independent validation cohort. Future studies are warranted to validate these findings in larger, multicenter cohorts. This finding aligns with that of Liu et al., who reported that KIM-1 is a robust biomarker for AKI with high sensitivity and specificity.[35]

IL-18, a pro-inflammatory cytokine, plays a crucial role in the immune response to renal injury by activating the inflammasome pathway, leading to tubular apoptosis and exacerbating kidney damage.[13,36] The elevated IL-18 in our study are consistent with previous evidence linking IL-18 to ischemic AKI and its role as a biomarker of systemic inflammation.[14,37] The positive correlation of IL-18 with serum creatinine and the negative correlation with eGFR in our study further substantiates its diagnostic relevance.

Our logistic regression analysis confirmed that KIM-1 and IL-18 were independent predictors of adverse clinical outcomes in patients with CRS. KIM-1 demonstrated the highest predictive strength with an odds ratio of 3.5, indicating a strong association between elevated KIM-1 levels and unfavorable outcomes. This finding is consistent with that of Zhang et al., who identified KIM-1 as a significant predictor of progression to CKD and adverse outcomes in patients with AKI. IL-18 has also emerged as an independent predictor, albeit with a weaker association, which may reflect its role as a systemic inflammatory marker rather than a direct indicator of tubular damage.[37,38] This distinction highlights the multifaceted nature of CRS, in which both structural and inflammatory processes interact to determine patient outcomes.

The high area under the ROC (AUC=0.971) and the classification accuracy (91.11%) achieved by our predictive model suggest that incorporating KIM-1 and IL-18 into clinical workflows could substantially enhance the precision of CRS diagnosis and prognosis. This aligns with the contemporary shift in nephrology and cardiology towards adopting biomarker-based approaches for the early detection of high-risk patients.[39]

The robust correlations among the parameters of KIM-1, IL-18, and renal function offer significant pathophysiological information about CRS. The strong positive correlation with serum creatinine and a negative correlation with eGFR underscores its close association with tubular injury and impaired filtration capacity. Similarly, IL-18's significant correlations with both renal function and systemic inflammation highlight its dual role in mediating kidney damage and orchestrating immune responses.[40] The inverse relationship between eGFR and both biomarkers emphasizes the intricate interplay between declining filtration capacity and progressive renal damage in CRS. These findings suggest that KIM-1 and IL-18 could serve not only as diagnostic tools, but also as surrogate markers to monitor disease progression and therapeutic efficacy. This dual functionality aligns with the principles of precision medicine, advocating personalized therapeutic strategies based on individual biomarker profiles.[41,42] Recent studies have also investigated emerging biomarkers such as NGAL, cystatin C, and soluble ST2 for CRS.[43,44] Although our study focused on KIM-1 and IL-18, future comparative analyzes are needed to determine their relative performance and potential for integration into clinical practice.

These findings have profound clinical implications. Early detection of acute CRS using biomarkers such as KIM-1 and IL-18 can facilitate timely therapeutic interventions, including optimizing volume status, managing neurohormonal activation, and mitigating inflammation. Moreover, these biomarkers can inform personalized treatment strategies by stratifying patients according to disease severity. For example, KIM-1's sensitivity to tubular injury can identify patients who may benefit the most from renal protective therapies, while IL-18 can aid in monitoring the efficacy of anti-inflammatory treatments. Integrating these biomarkers into clinical practice aligns with evolving paradigms in precision medicine, which prioritize individualized risk stratification and therapeutic approaches in the management of complex syndromes such as CRS.[45,46] Furthermore, the use of KIM-1 and IL-18 can improve the early identification of high-risk patients, potentially improving clinical outcomes and reducing the healthcare costs associated with delayed diagnosis and treatment. Our results are in line with recent reports that highlight the promise of biomarker-guided approaches for early

detection and personalized management in renal dysfunction.[47] Despite the promising diagnostic and prognostic potential of plasma KIM-1 and IL-18, several practical barriers remain. These include the cost-effectiveness of routine biomarker measurement, the need for standardized assay protocols in clinical laboratories, and regulatory hurdles that can affect widespread clinical adoption. Addressing these issues will be critical to a successful translation into daily clinical practice.

Study limitations and strengths

One of the main strengths of this study was the comprehensive evaluation of traditional renal biomarkers (serum creatinine) and a new marker of tubular injury (KIM-1) in an acute cardiorenal population. By correlating baseline and current creatinine levels with KIM-1, our findings provide more insight into the pathophysiology of AKI in the setting of heart failure. Furthermore, the use of standardized analytical techniques and well-defined clinical groups strengthened the internal validity of our results. Despite these compelling findings, this study has several limitations. The case-control design restricts our ability to draw causal inferences regarding biomarker dynamics and disease progression. Longitudinal studies are essential to validate the temporal relationships between KIM-1 and IL-18 levels and clinical outcomes in CRS. A major limitation of our study is the small sample size (n=30 per group), which can increase the risk of overfitting and limit the generalizability of our findings. Future studies with larger, multicenter cohorts are needed to confirm these results.

Future directions

Future research should explore the interaction between cardiac biomarkers (eg, NT-proBNP) and renal biomarkers to provide a more holistic understanding of the pathophysiology of CRS. Investigating the combined prognostic value of these biomarkers could reveal the complex interdependencies between cardiac and renal dysfunctions. Future research should include an independent validation cohort to verify the diagnostic and prognostic performance of these biomarkers. Moreover, evaluating the cost effectiveness and feasibility of integrating KIM-1 and IL-18 into routine clinical workflows is crucial to their widespread adoption. Although our findings are promising, future studies involving larger and more heterogeneous cohorts over extended time frames are essential to validate the diagnostic and prognostic functions of these biomarkers and to ensure their effective integration into clinical practice. Furthermore, our study represents a single time-point analysis. Future research should include serial measurements of plasma KIM-1 and IL-18 to better elucidate their temporal dynamics during disease progression and recovery.

Conclusion

This study highlights the clinical utility of plasma KIM-1 and IL-18 levels as diagnostic and prognostic biomarkers for acute CRS. Their strong association with renal dysfunction and adverse disease outcomes underscores their potential to enhance risk stratification, facilitate early diagnosis, and inform personalized treatment strategies. These findings contribute to the growing evidence supporting biomarker-based approaches in the management of cardiorenal syndromes, paving the way for more precise and effective care in this high-risk patient population.

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Declarations

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Author contributions

Conceptualization, R.D.A and H.A.F; Methodology, R.D.A; Software, R.D.A and K.H.H.; Validation, R.D.A., H.A.F. and K.H.H.; Formal Analysis, R.D.A.; Investigation, R.D.A.; Resources, R.D.A and K.H.H; Data Curation, R.D.A.; Writing – Original Draft Preparation, R.D.A; Writing – Review & Editing, H.A.F.; Visualization, K.H.H.; Supervision, H.A.F.; Project Administration, H.A.F and R.D.A.; Funding Acquisition, H.A.F.

Conflicts of interest

The author declare that they have no competing interests.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

Ethical clearance was granted by the Institutional Review Board of the Medical Laboratory Techniques, College of Health and Medical Techniques at Al-Furat Al-Awsat Technical University, Al-Kufa, Iraq (Approval Number: 34328).

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